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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/055,797	01/22/2002	David Beach	CSHL-P03-010	7431

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/055,797	BEACH ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/17/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,49 and 83-124* is/are pending in the application.

4a) Of the above claim(s) *48 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/02/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 12/17/2004 is acknowledged. The traversal is on the ground(s) that Group I (claims 48-82 and 88-91), which is directed to a method of attenuating expression of a target gene using dsRNA, is closely related to Group II. Applicants note that both Group I and Group II are classified in class 514, subclass 44 and therefore simultaneous examination of the pending claims of both groups would not impose a substantial additional burden on the Examiner. Applicants quote a citation from MPEP 803 and submit that there is no significant additional burden on the Examiner to search Group I together with the elected Group II. Applicant concludes that reconsideration and withdrawal of the restriction requirement are respectfully requested.

The arguments have been thoroughly reviewed and considered, however they are not found persuasive because the class 514, subclass 44 encompasses multiple inventions. Further, the classification of inventions does not completely reflect the search burden because searching the above inventions requires a search of the non patented literature. Therefore, the inventions are distinct for the reasons set forth in the Office Action filed on 6/30/2004. The requirement is still deemed proper and is therefore made FINAL.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date is determined to be that of the provisional application of 60/243,09, which has a filing date of 10/24/2000. The instant case 10/055,797 does not receive the benefit of the earlier filing date of the provisional application 60/189,739 filed on 03/16/2000 because claims 83-124 of the instant case are not supported by the specification and claims of the previously mentioned application.

The provisional application 60/189,739 discloses methods of gene silencing in cells provoked by a double-stranded RNA (dsRNA) that is sequence specific to a target gene. Although the provisional application discloses a method of attenuation of a target gene using dsRNA, the provisional application does not disclose a method of attenuation of a target gene using a variegated library of single-stranded hairpin ribonucleic acid (RNA) species. Thus the instant application has an effective filing date of 10/24/2000.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 95-98 and 101 are provisionally rejected under the judicially created doctrine of double patenting over claim 25-28 of copending Application No. 10/350,798. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 25-28 of '798 application has overlapping scope with claims 95-98 and 101 of the instant application.

Claims 25-28 of '798 are drawn to a method for generating a variegated library of short interfering double-stranded RNA (siRNA) by providing an *in vitro* transcription system which uses a RNA polymerase. Claims 95-98 and 101 of the instant application are drawn to producing a variegated library of hairpin RNA which is transcribed *in vitro* and utilizes a RNA polymerase. Therefore, claims 25-28 of '798 have the same limitations as claims 95-98 and 101 of the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 83-124 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US Patent Number 6,506,559).

Claim 83 is drawn to a method of attenuating expression of one or more target genes in mammalian cells comprising introducing into the cells a library of single-stranded RNA. Claim 84 limits claim 83 by reciting the library of single-stranded RNA attenuate expression of a plurality of different target genes. Claims 85-86 limit claim 83 by reciting the library of hairpin RNA species is arrayed on a solid support. Claims 87 further limits claim 83 by including a step of identifying hairpin RNA species which produce a detected phenotype in cells. Claims 90-94 limit claim 83 by reciting the hairpin RNA is chemically synthesized, is an *in vitro* transcription product, is transfected into cells, is microinjected and is a transcriptional product transcribed from an expression construct, respectively. Claims 95-99 and 101 limit claim 83 by reciting the hairpin RNA includes a promoter for cellular RNA polymerase the RNA is a transcriptional product of the polymerase. Claim 100 further limits claim 94 by reciting the hairpin RNA is stably transfected. Claims 102-108 limit claim 83 by reciting the cells are germ line cells, stem cells, somatic cells, immortalized cells, primate cells, human cells or selected from a group as listed in claim 108. Claims 109-110 further limit claim 83 by reciting the hairpin RNA is introduced into the cells in cell culture or in an animal. Claims 110-112 limit claim 83 by reciting expression of the target is attenuated by at least 33 or 90 percent relative expression, respectively. Claims 113-115 limit claim 83 by reciting the target gene is an endogenous gene, a

heterologous gene or a gene of a pathogen. Claims 116-120 limit claim 83 by reciting the self-complementary sequences hybridize under intracellular conditions. Claims 121-22 limit claim 83 by reciting the hairpin RNA contains a modified backbone and wherein the modifications inhibit inactivation of the RNA. Claims 132-124 further limit claim 83 by reciting the self-complementary sequences are 20-50 nucleotides in length or 29 nucleotides in length.

Fire et al. disclose a method of attenuating expression of a target gene in mammalian cells comprising a library of duplex RNA (see column 12, lines 49-54). Fire et al. further discloses this duplex RNA is a double-stranded structure that may be formed by a single self complementary RNA strand or two complementary RNA strands that can form a RNA duplex inside or outside the cell (see column 4, lines 44-48). The library of duplex RNA can be arrayed on a solid support or wells of a microtiter plate (see column 12, lines 55-61). The duplex RNA can have a modified backbone (see column 7, line 32) and is a transcriptional product of a RNA polymerase (see column 4, lines 64-68). Fire et al. further discloses the target gene can be an endogenous gene or a pathogen (see column 6, lines 44-51) and the cells having the target gene may be from the germ cell line, somatic cell line, stem cell line or immortalized cell line (see column 8, line 52-62). Fire et al. does not disclose a nucleotide length limitation or disclose a necessary degree of attenuation of the target gene. Therefore, the scope encompasses all nucleotide lengths and degrees of attenuation and would anticipate the limitations of the instant claims.

Thus, Fire et al. anticipates claims 83-124 of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 83-124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of attenuating expression of one or more target genes using a dsRNA in mammalian cells *in vitro*, does not reasonably provide enablement for a method of attenuating expression of one or more target genes using a dsRNA or a library of single-stranded RNA in mammalian cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method for method of attenuating expression of one or more target genes using a library of single-stranded hairpin RNA in mammalian cells *in vitro*. Further the instant claims recite that each hairpin RNA species comprises self-complementary sequences of 19 to 100 nucleotides that form duplex regions and which hybridize under intracellular conditions to a target gene.

The specification as filed discloses suppression of gene expression in several human or murine cell lines using a long dsRNA (see Example 4) or using a short hairpin dsRNA (see Example 6). The specification further discloses that dsRNA suppression does not elicit a PKR response (see Example 8) and that suppression of a target gene using dsRNA which corresponds to a non-coding region of the target gene (see Example 9). The specification does not teach a

method of attenuating expression of one or more target genes using dsRNA or a library of single-stranded hairpin RNA in mammalian cells *in vivo.*

There is no guidance in the specification as filed that teaches how to target the claimed library of single-stranded hairpin RNA to mammalian cells or tissues *in vivo* or attenuate the expression of specific target genes of mammalian cells or tissues *in vivo*. Although the specification discloses suppression of gene expression in several human or murine cell lines using long dsRNAs *in vitro* by administration of dsRNAs, such a disclosure would not be considered enabling since the state of RNAi-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 83-124 encompass methods of attenuating expression, *in vivo*, in a broad range of target genes in different tissues by use of a library of single-stranded hairpin RNA. Although the specification discloses suppression of gene expression in several human or murine cell lines using long dsRNAs *in vitro* by administration of dsRNAs (see Examples 4 and 6), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using RNAi at the time of filing of the instant application. Ui-Tei et al. (FEBS 2000, 479:79-82) teaches gene suppression in mammalian cells was very unpredictable and had

only limited success using RNAi in mammalian cells (see page 81 Figure 3). Caplen et al. (Gene 2000, 252:95-105) further provide evidence of the unpredictability of gene suppression in a study where they "examined three different mammalian cells...using a range of does of dsRNA...[and] saw no specific effect on gene expression" (see page 103 first full paragraph). Caplen states that "it may be that gene, cell-type or developmentally specific effects may influence the balance between specific (PTGS) and non-specific responses to dsRNA. This would need to be taken into account when considering PTGS or RNAi in mammalian cell systems" (see page 103 first full paragraph).

Recent publications illustrate the ongoing difficulties for therapeutic *in vivo* applications using RNAi. Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) states that "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). Novina et al. (Nature 2004, Vol.430:161-164) agrees that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph).

Paroo et al. (Trends in Biotechnology 2004, Vol.22(8):390-394) summarizes by stating "[d]eveloping siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles.

However, the duplex nature of siRNA introduced an additional layer of complexity. Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for in vivo experiments or therapeutic development. Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

As outlined above, it is well known that there is a high level of unpredictability in the RNAi art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely attenuating expression of a target gene *in vivo* using a library of dsRNA.

While one skilled in the art may be able to produce a library of dsRNA targeted to one or more genes and attenuate expression of mammalian cells *in vitro*, the specification as filed does not teach how to attenuate expression of one or more target genes *in vivo* using a library of dsRNA, as claimed. Further, the specification as filed does not teach how to attenuate expression of one or more target genes *in vivo* using a library of dsRNA.

Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) supports the difficulties of extrapolating from in vitro experiments and states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in*

vitro uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

In view of the unpredictability in the art of RNAi-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of the library of hairpin RNA *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the hairpin RNA *in vivo*, delivery of the hairpin RNA to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "variegated" in claims 83-124 is a relative term which renders the claim indefinite. The term "variegated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "variegated" is not an art recognized

term for describing a library of RNA species. Further, it is unclear what is encompassed in the library because the metes and bounds of the term "variegated" are unclear. Clarification is required.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

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